Articles in PresS. J Appl Physiol (April 30, 2015). doi:10.1152/japplphysiol.00176.2015

Heat acclimation improves heat exercise tolerance and heat dissipation in individuals with extensive skin grafts

Zachary J. Schlader*[,1,2], Matthew S. Ganio*[,1,3], James Pearson[1,4], Rebekah A.I. Lucas[1,5], Daniel Gagnon[1], Eric Rivas[1,6], Karen J. Kowalske[7], Craig G. Crandall[1]

[1] Institute for Exercise and Environmental Medicine, Texas Health Presbyterian Hospital of Dallas, TX, USA and Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, TX, USA

[2] Department of Exercise and Nutrition Sciences, University at Buffalo, Buffalo, NY, USA

[3] Department of Health, Human Performance, and Recreation, University of Arkansas, Fayetteville, AR, USA

[4] Department of Biology, University of Colorado at Colorado Springs, Colorado Springs, CO, USA

[5] School of Sport, Exercise and Rehabilitation Sciences, University of Birmingham, Birmingham, UK

[6] Department of Kinesiology, Texas Woman's University, Denton, TX, USA

[7] Department of Physical Medicine and Rehabilitation, University of Texas Southwestern Medical Center, Dallas, TX, USA

* Contributed equally to this study and should be viewed as co-first authors

Corresponding Author:
Craig G. Crandall, PhD
Institute for Exercise and Environmental Medicine
7232 Greenville Ave
Dallas, TX, 75231, USA
Email: CraigCrandall@texashealth.org
Phone: 214-345-4623

Running Head: Heat acclimation in burn survivors
Word Count: 4599
Abstract Word Count: 246
Number of References: 61
Number of Tables: 1
Number of Figures: 6

Abstract

Burn survivors with extensive skin grafts have impaired heat dissipation and thus heat tolerance. This study tested the hypothesis that heat acclimation (HA) improves these factors in this population. Thirty-four burn survivors were stratified into highly (>40% body surface area (BSA) grafted, n=15) and moderately (17-40% BSA grafted, n=19) grafted groups. Nine healthy non-burned subjects served as controls. Subjects underwent 7 days of HA involving 90 min of exercise at ~50% peak oxygen uptake in 40°C, 30% RH. On days 1 and 7, subjects exercised in the heat at a fixed rate of metabolic heat production. Pre-HA, all controls and 18/19 subjects in the 17-40% group completed 90 min of exercise. Conversely, heat exercise tolerance was lower ($P<0.01$) in the >40% group, with 7/15 subjects not completing 90 min of exercise. Post-HA, heat exercise tolerance was similar between groups ($P=0.39$) as all subjects, except one, completed 90 min of exercise. Pre-HA, the magnitude of the increase in internal temperature during exercise occurred sequentially ($P\leq0.03$) according to BSA grafted (>40%: 1.6 ± 0.5°C, 17-40%: 1.2 ± 0.3°C, control: 0.9 ± 0.2°C). HA attenuated ($P<0.01$) increases in internal temperature in the control (by 0.2 ± 0.3°C), 17-40% (by 0.3 ± 0.3°C), and >40% (by 0.3 ± 0.4°C) groups, the magnitude of which was similar between groups ($P=0.42$). These data indicate that HA improves heat tolerance and dissipation in burn survivors with grafted skin and the magnitude of these improvements are not influenced by the extent of skin grafting.

Keywords: heat tolerance, hyperthermia, burn injury, skin grafting, heat adaptation, heat loss

Introduction

Between 5 and 20% of all military battlefield injuries are burn related (8, 60), while in the United States 40,000-70,000 civilians per year are hospitalized for burn-related injuries (11), with ~16% of these cases involving burns covering >20% of the total body surface area (BSA) (2). Twenty years ago, burns covering half of a person's BSA were fatal. However, due to medical advances, patients with upwards to 90% BSA burned are now surviving (52). Serious burns permanently damage the skin, requiring, in most cases the damaged tissue to be excised and replaced with grafted skin. This grafted skin impedes heat dissipation (25). Owing to physical disruption of the sweat glands and/or ducts, sweat production in grafted skin is virtually non-existent during heat stress, compared to ungrafted skin, while increases in skin blood flow are markedly attenuated (16), due to compromised re-innervation and/or responsiveness of cutaneous active vasodilator nerves (15). Importantly, these impairments persist at least 8 years post-injury and may, in fact, be permanent (17). As a result, burn survivors with grafted skin have greater increases in internal temperature during exercise in the heat when compared to unburned individuals (4, 27, 54). Interestingly, those with the greatest BSA grafted have the greatest increases in internal temperature (27), suggesting that the ungrafted skin does not fully compensate for the impaired heat loss in grafted skin. Thus, burn survivors with grafted skin, especially those with a high BSA grafted, are relatively heat intolerant (35) and are likely at an elevated risk for hyperthermia and heat-related injuries (47).

Repeated exposure to heat and subsequent hyperthermia, typically involving exercise in the heat, evokes the process of heat acclimation (HA) (49, 56). Primarily through enhancements in skin blood flow (23, 34, 37-39, 45) and sweating (23, 34, 37, 39, 45, 61), HA improves heat dissipation (44), which results in less of an increase in internal temperature for a given thermal load (37-39, 45, 46, 61) and permits functional improvements in exercise tolerance and performance in the heat (21, 33, 38, 39). These adaptations occur relatively rapidly, with ~70% of the total heat acclimation response occurring in just 7 days (21, 44, 46), and the remaining occurring within ~14 days (44, 56). Thus, even short-term HA is a valuable strategy for improving heat tolerance and reducing the risk and incidence of hyperthermia and heat-related injuries (5, 10).

A case study conducted by our laboratory suggested that a short-term, 7 day HA regimen in a burn survivor with a high BSA of grafted skin (~75% BSA grafted) is capable of improving heat dissipation, thereby attenuating increases in internal temperature (59). Whether these findings are consistent in a larger group of burn survivors, with a varying extent of grafted skin, remains uncertain. Therefore, this study tested the hypothesis that a 7 day HA regimen improves heat exercise tolerance and heat dissipation in burn survivors with grafted skin. The information gained from this study will aid clinicians and their patients in understanding the effects of serious burn injuries, and subsequent skin grafting, on whether short-term HA is an effective strategy to improve heat tolerance, safety, and comfort in hot environments that are typically encountered during both work and recreation.

Methods

Thirty-four otherwise healthy burn survivors with grafted skin and nine non-burned control subjects completed this study. The burn survivors were stratified into two groups based upon their BSA grafted: 17-40% (n=19) and >40% (n=15). The subject characteristics are listed in Table 1. All subjects were free of any known cardiovascular, metabolic, neurological, or psychological diseases. Subjects taking medications known to affect the cardiovascular system and/or heat dissipation were excluded. Burn survivors were at least 12 months removed from their last surgery. Each subject was fully informed of the experimental procedures and possible risks before giving informed, written consent. This protocol and consent were approved by the Institutional Review Boards at the University of Texas Southwestern Medical Center at Dallas and Texas Health Presbyterian Hospital of Dallas. For each visit, subjects arrived at the laboratory euhydrated (confirmed via urine specific gravity: 1.015 ± 0.008) and having refrained from strenuous exercise, alcohol and caffeine for a period of 12 h. Subjects were recruited from throughout North American with testing completed in the northern hemisphere (Dallas, Texas, USA) during the fall, winter, and spring months. A portion of these data have been presented in a previously published manuscript that tested unique hypotheses (27).

Instrumentation and measurements

Total BSA was calculated from height and weight (20), while the percentage of BSA grafted was calculated using the Rule of Nine's (48). Together, the absolute BSA ungrafted for each subject was calculated from total BSA and the percent BSA grafted. At least 60 min, but usually more than 8 h, prior to experimental testing, each subject swallowed a telemetry pill (HQ Inc., Palmetto, FL, USA) for the measurement of internal temperature. Three subjects had contraindications for taking the telemetry pill. In these subjects esophageal (n=1) or rectal (n=2) temperature was measured. Esophageal temperature was measured at a depth of ~40 cm (36), while rectal temperature was measured at a depth ~10 cm past the anal sphincter using general purpose thermocouples (Mon-a-therm, Mallinckrodt Medical, Inc., St. Louis, MO, USA). Given the difficulty in accurately quantifying mean skin temperature using a reasonable number of locations and using the same ungrafted and grafted skin locations in all individuals with grafted skin, skin temperature was measured from a single ungrafted (all subjects) and grafted (burn survivors only) location. The location of these thermocouples was maintained constant, within a subject, throughout all measurement periods, and was usually placed on the upper arm, chest or back depending on the location of skin grafting. Heart rate was measured using a Polar heart rate monitor (Polar Electro, Kempele, Finland). On separate days pre- and post- HA (see below), blood and plasma volumes were measured via the carbon monoxide rebreathing method described previously in detail (28) following at least 30 min of recumbent rest. Whole-body sweat rate was measured via pre- to post- exercise nude body weight measurements, corrected for fluid consumption and urine output. Ratings of perceived exertion (RPE) were measured using a standard Borg scale (from 6-20) (6). Thermal perception was measured on a modified 5 point scale where, 4 is described as “Neutral (Comfortable)” and 8 as “Unbearably Hot”, with 0.5 increments (57). The rate of metabolic heat production (H_{prod}) was calculated from oxygen uptake, the respiratory exchange ratio (Parvo Medics, Sandy, UT, USA), and the rate of external work (40). Sweat sodium, potassium, and chloride concentrations were measured in duplicate on ungrafted skin locations using the regional patch method (3). The location of these sweat patches was maintained constant within a subject throughout all measurement periods.

Experimental protocol

Subjects visited the laboratory on 9 days within a 9 to 10 day period. On visit 1, peak oxygen uptake was measured using methods described previously in our laboratory in this population (26). On visits 1 and 9, carbon monoxide rebreathing procedures were carried out for blood volume determination. During the middle 7 visits, subjects underwent a HA regimen over 7-8 days (subjects were given the option to have one day off in the middle of the regimen). The HA regimen involved 7 days of exercise in a 39.6 ± 1.1°C, 31 ± 3% RH environment. Subjects exercised either on a cycle ergometer or walked on a treadmill. During all trials a fan was directed at the subjects which provided an air velocity of ~3 m/s. Subjects drank 12 ml/kg of warmed (37.1 ± 1.4°C) water throughout exercise (total volume: 951 ± 173 ml). The timing of drinking was carefully controlled such that no fluid was permitted within 5 min of measuring internal temperature. This was done to avoid temperature fluctuations in internal temperature due to the consumption of water, which was confirmed by continually monitoring internal temperature throughout the exercise, including during drinking. On days 1 and 7 of the HA regimen, subjects underwent a heat exercise test during which they exercised at a fixed H_{prod}, expressed both as absolute and relative to body mass (Figure 1). This was employed to isolate, independent of physical fitness (31) or body weight (14), the influence of grafted skin on absolute sweat production (absolute H_{prod}) (24) and the increase in internal temperature (relative H_{prod}) (14) during exercise. During these heat exercise tests, subjects exercised for 90 min and had the option for a short (5 ± 3 min) break at 45 min. Subjects exercised for the full 90 min unless they reached volitional exhaustion or their internal temperature achieved 39.5°C. Within subjects, the day 7 (post-HA) heat exercise test employed the exact same external workload, exercise modality, rest period duration, fluid consumption, etc. as that occurring during the day 1 (pre-HA) heat exercise test. On days 2-6, in order to account for slight differences in aerobic fitness, subjects exercised for 90 min at 53 ± 7% of peak oxygen uptake (1.2 ± 0.4 L/min).

Data and statistical analyses

With the exception of blood and plasma volume data (see above), data are presented only from the heat exercise tests conducted pre- (day 1) and post- (day 7) HA, in order to identify the effect of HA on heat exercise tolerance and heat dissipation. Whole-body sweat rate is expressed in absolute terms (in L/h) and as sweat rate relative to the increase in internal temperature during the exercise bout (in

L/h/°C). Given that grafted skin does not measurably produce sweat during heat stress (16), both indices were also expressed relative to the absolute BSA of ungrafted skin (in L/h/m^2 and L/h/°C/m^2).

Subject characteristics were analyzed using one-way analysis of variance (ANOVA), while data pre- and post- HA were analyzed using a two-way mixed model ANOVA (group x HA). Where appropriate, *post hoc* Holm-Sidak pair-wise comparisons between independent groups were made. Kaplan-Meier curves with log-rank tests were used to quantify differences in heat exercise tolerance between groups both pre- and post- HA. Data were analyzed using GraphPad Prism (6, GraphPad Software, Inc., La Jolla, CA, USA). A priori statistical significance set at $P \leq 0.05$, but actual p-values are reported where possible. All data are reported as mean ± SD.

Results

Absolute and relative H_{prod} were not different (P≥0.390) between groups both pre- and post- HA (Figure 1). However, H_{prod} was, on average, 12 ± 36 W and 0.2 ± 0.5 W/kg lower (P≤0.030) post- HA (Figure 1).

Heat exercise tolerance

Pre-HA, all nine of the controls and all but one (of 19) in the 17-40% group (due to volitional exhaustion) were able to complete the full 90 min of exercise (Figure 2). By contrast, heat exercise tolerance was lower (P=0.002) in the >40% group (Figure 2), with only eight (of 15) subjects completing the 90 min of exercise (internal temperature ≥39.5°C: n=3; volitional exhaustion: n=4). Post-HA, all subjects were able to complete the 90 min of exercise, except for one subject in the >40% group (Figure 2), in which exercise was terminated due to the attainment of an internal temperature ≥39.5°C.

Body temperature

Pre-exercise internal temperature was not different between groups (P=0.291) and was unaffected by HA (P=0.431) (mean - Pre-HA: 37.1 ± 0.4°C, Post-HA: 37.1 ± 0.4°C). Pre-HA, the increase in internal temperature during exercise was greatest (P≤0.005) in the >40% group, and lowest (P≤0.031) in the control group, while the 17-40% group was in the middle (Figure 3). HA attenuated (P<0.001) the increase in internal temperature during exercise by 0.2 ± 0.3°C (control), 0.3 ± 0.3°C (17-40%), and 0.3 ± 0.4°C (>40%). However, the magnitude of these attenuations did not differ between groups (group x HA interaction: P=0.417) (Figure 3). Ungrafted skin temperature was lower (P=0.004) following HA, but grafted skin temperature was unaffected (P=0.163) (Figure 3).

Cardiovascular adjustments

Pre-exercise heart rate was not different between groups (P=0.938) and was not different following HA (P=0.086) (mean - Pre-HA: 87 ± 11 bpm, Post-HA: 85 ± 11 bpm). Pre-HA, heart rate at the end of exercise was higher (P=0.006) in the >40% group compared to both the 17-40% and control groups, between which there was no difference (P=0.466) (Figure 4). HA resulted in a lower (P<0.001) heart rate at the end of exercise, but the magnitude of these changes did not differ between groups (group x HA interaction: P=0.199) (Figure 4). Blood volume was similar (P=0.586) between groups (control: 78 ± 5 ml/kg, 17-40%: 73 ± 11 ml/kg, >40%: 77 ± 12 ml/kg) and did not change (P=0.073) with HA (control: 80 ± 10 ml/kg, 17-40%: 76 ± 14 ml/kg, >40%: 79 ± 14 ml/kg). Plasma volume was also similar (P=0.282) between groups and increased (P=0.011) with HA, although the magnitude of this improvement was similar between groups (group x HA interaction: P=0.839) (Figure 4).

Sweating

Absolute whole-body sweat rates were similar (P=0.198) between groups and did not change (P=0.254) with HA (Figure 5). When whole-body sweat rate was expressed relative to the absolute BSA of ungrafted skin (i.e., the surface area available to sweat), sweat rate was greatest (P≤0.022) in the >40% group (Figure 5). Pre-HA, absolute sweat rate relative to the increase in internal temperature was lower (P=0.027) in the >40% group compared to the control group (Figure 5). This measure of sweat rate increased (P≤0.005) with HA (Figure 5), but remained lowest (P≤0.038) in the >40% group and was highest (P≤0.049) in the control group (Figure 5). The magnitude of these HA induced changes did not differ between groups (group x HA interaction: P=0.513). Sweat rate relative to the increase in internal temperature, when expressed relative to the absolute BSA of ungrafted skin, was not different (P=0.792) between groups and increased (P<0.001) with HA, the magnitude of which did not differ between groups (group x HA interaction: P=0.923) (Figure 5). Sweat sodium concentration decreased (P=0.025) with HA, but the magnitude of this reduction did not differ between groups (group x HA interaction: P=0.347, mean - Pre-HA: 97 ± 23 mmol/L, Post-HA: 85 ± 33 mmol/L). In contrast, sweat potassium (mean - Pre-HA: 8 ± 1 mmol/L, Post-HA: 8 ± 1 mmol/L, P=0.615) and chloride (mean - Pre-HA: 78 ± 14 mmol/L, Post-HA: 71 ± 21 mmol/L, P=0.102) concentrations did not change with HA.

Perceptual measures

Pre-HA, RPE was higher at the end of exercise in the >40% group (17 ± 3 a.u., ~'very hard') compared to the control (14 ± 2 a.u., between 'somewhat hard' and 'very hard', P=0.023) and 17-40% groups (13 ± 3 a.u., 'somewhat hard', P=0.004), which were similar (P=0.859) (Figure 6). Post-HA, RPE was lower (P=0.001) at the end of exercise, with the magnitude of reductions in RPE being not different between groups (group x HA interaction: P=0.780) (Figure 6). Thermal perceptions immediately before exercise were perceived as 'warm', which was similar between groups (P=0.669) and did not change (P=0.322) with HA (mean - Pre-HA: 5.1 ± 0.1 a.u., Post-HA: 5.0 ± 0.1 a.u.). At the end of exercise, pre-HA perceptions of warmth were higher in the >40% group (7.2 ± 0.7 a.u., ~'very hot') compared to the control group (5.8 ± 0.8 a.u., ~'hot', P=0.006), both of which were not different from the 17-40% group (6.4 ± 1.1 a.u., between 'hot' and 'very hot', P≥0.084) (Figure 6). Post-HA, warmth perceptions were lower (P=0.001) at the end of exercise in all groups and the magnitude of this attenuation did not differ between groups (group x HA interaction: P=0.165) (Figure 6).

Discussion

This study tested the hypothesis that a 7 day HA regimen involving 90 min of exercise at ~50% of peak oxygen uptake in a hot (~40°C) and dry (~30% RH) environment improves heat exercise tolerance and heat dissipation in burn survivors with grafted skin. In support of this hypothesis, thirty-three (of 34) burn survivors with grafted skin completed the entire 90 min of exercise following HA, compared with just 26 (of 34) before HA (Figure 2). At least partially explaining these observations, increases in internal temperature during exercise were attenuated following HA (Figure 3), suggesting that heat dissipation was enhanced. Interestingly, the magnitude of this improvement in heat dissipation was not different between groups. This finding is supported by similar enhancements in cardiovascular (Figure 4), sweating (Figure 5), and perceptual (Figure 6) responses with HA between groups. Collectively, these data indicate that a 7 day HA regimen improves heat exercise tolerance and heat dissipation in burn survivors with grafted skin and that the magnitude of this improvement is not influenced by the extent of grafted skin. These findings suggest that, with the HA regimen employed herein, the degree of adaptation with HA in ungrafted skin is independent of the BSA available for heat dissipation.

Improved heat exercise tolerance

Exercise tolerance in the heat is compromised in child burn survivors (35). The current study extends these findings to adult burn survivors, such that pre-HA heat exercise tolerance, defined as the ability to complete the 90 min of exercise in a hot and dry environment, was lowest in the group of burn survivors with the greatest extent of skin grafting (i.e., >40% group) (Figure 2). More importantly, however, we demonstrated that heat exercise tolerance can be dramatically improved following HA (Figure 2). Although novel, this finding is not necessarily surprising as improvements in exercise tolerance (13, 21, 38, 39) and performance (33) are typically observed following HA in healthy subjects. The mechanism(s) underlying this observation are likely multifactorial, perhaps mediated by attenuated increases in internal temperature during exercise (Figure 3) that led to lower sensations of warmth and perceived exertion during exercise (Figure 6), which are known to influence exercise tolerance in the heat (51).

Improved heat dissipation

Heat dissipation improves with 7 days of HA (44). Evidence of this improvement is demonstrated by a lower internal temperature for a given thermal load (37-39, 45, 46, 61). In the present study, exercise was carried out at a fixed H_{prod}, expressed as both absolute and relative to body mass, between subjects (Figure 1). This is an important consideration. The similar absolute H_{prod} ensured the same stimulus for absolute whole-body sweat production (24, 31), while the similar H_{prod} relative to body mass ensured that any differences in internal temperature between groups were due to differences in heat dissipation (14). Using this approach, we (25, 27), and others (4, 54), have demonstrated that burn survivors with grafted skin have impaired heat dissipation, and that the magnitude of this impairment is greatest in those with the highest BSA grafted (Figure 3, Pre-HA). The current study extends these findings, and others from our laboratory (59), by demonstrating that heat dissipation is improved in a large group of burn survivors with varied percentages of BSA of grafted skin following a 7 day HA regimen (Figure 3).

It is notable that, although H_{prod} was not different between groups at any time point, we did observe a small, but statistically significant reduction in H_{prod} (by ~12 W or ~0.2 W/kg) following HA (Figure 1). This is probably because the external workload was the same pre- and post- HA and there were slight improvements in exercise economy, i.e., slightly lower H_{prod} for a given external workload, post-HA (13, 21, 50). In the current study, the average attenuation in the increase in internal temperature during exercise following HA was -0.3 ± 0.3°C (Figure 3). Recent evidence indicates that, in order to achieve differences in internal temperature of a similar magnitude (~0.4°C), H_{prod} (relative to body mass) would have to have been attenuated ~10 fold more than what we observed (~2.0 vs. ~0.2 W/kg) to fully account for the attenuated increases in internal temperature observed post-HA in this study (14). In support of this contention, post hoc correlational analysis indicates that changes in H_{prod} pre- to post- HA accounts for 9-10% of the variance in the attenuated rise in internal temperature observed post- HA (H_{prod} in W: R^2=0.09, H_{prod} in W/kg: R^2=0.10). Thus, it is unlikely that subtle differences in H_{prod} explain the attenuated increases in internal temperature following HA (Figure 3). Rather, it is likely that heat dissipation was enhanced, as evidenced by improvements in sweating for a given increase in internal temperature following HA (Figure 5).

Factors mediating improvements in heat dissipation following HA are numerous and include improvements in sweating (23, 34, 37, 39, 45, 61) and skin blood flow (23, 34, 37-39, 45), reduced sweat electrolyte concentrations (1, 19), and increased plasma volume (38, 41, 53). Ultimately, these adaptations result in lower heart rates (37, 46), skin temperatures (33, 38), increases in internal temperature during exercise (38, 46, 55), and sensations of warmth (18, 32, 55) and perceived exertion (43, 58). In this light, the findings of the present study are hallmark of HA. That is, plasma volume increased (Figure 4), sweat sodium concentration decreased, and sweat rate relative to the increase in internal temperature was enhanced (Figure 5). These adaptations resulted in lower heart rates at the end of exercise (Figure 4), lower ungrafted skin temperatures (Figure 3), attenuated increases in internal temperature during exercise (Figure 3), and reduced perceptions of warmth and perceived exertion at the end of exercise (Figure 6).

Importantly, in the present study the magnitude of HA induced improvements in heat dissipation, in addition to the underlying adaptations, did not differ between groups (Figures 3-5). Rather, impairments in heat dissipation were still evident between groups following HA (Figure 3). This suggests that, in the current paradigm, the degree of adaptation with HA was independent of the BSA available for heat dissipation, and that the adaptions in the ungrafted skin of burn survivors were not enhanced such that impairments in heat dissipation between groups were abolished following HA. The observed improvements in sweating perhaps best highlight this point. That is, despite whole-body sweat rate not increasing with HA sweat rate for a given increase in internal temperature did improve (Figure 5); a finding that has been demonstrated previously (12, 38). Interestingly, although this absolute sweat rate response was impaired with increased skin grafting, the increase in sweat rate for a given increase in internal temperature in the ungrafted skin was not different between groups and improved similarly with HA in all groups (Figure 5). Thus, the ungrafted skin seemingly adapted to the same extent in all groups, independent of the BSA available for heat dissipation. This finding suggests that impairments in heat dissipation in burn survivors with grafted skin, even following HA, are due, primarily, to reductions in the BSA available for heat dissipation (i.e., grafted skin).

Unfortunately, the precise mechanisms underlying the improvements in heat dissipation cannot be discerned from the current study. That is, although classic adaptations indicative of HA were observed, the neural, structural, and/or chemical manner in which these adaptations were elicited remains uncertain. For instance, the augmentation of sweat rate relative to the increase in internal temperature with HA in the current study can be explained by a number of factors, including: 1) enhanced sensitivity of the 'central' neural control of sweating (37), i.e., a given change in temperature eliciting a greater neural drive to increase sweat production, 2) improvements in post-junctional sensitivity of the sweat glands (7, 30, 34), and/or 3) improvements in sweating efficiency such that more evaporation occurred for a given sweat rate. The latter of which may be due to improvements in the capacity to produce a skin wetness that is optimal for heat dissipation, e.g., by altering sweat distribution and/or reducing dripping (9). Regrettably, the current data do not allow for further speculation. Nevertheless, despite this lack of mechanistic insight, the importance of these findings, i.e., that burn survivors with grafted skin maintain the capacity to heat acclimate and that these adaptations improve heat tolerance, cannot be understated.

Methodological considerations

We chose 7 days of exercise in the heat to induce HA. This approach was chosen given that: 1) upwards to 70% of the improvements in heat dissipation occurs within the first 7 days (21, 44, 46), and 2) such an approach has a high external validity for clinicians and burn survivors. As a result, however, we may have underestimated the magnitude of improvements in heat dissipation compared to if we had used, for instance, a 14 day HA regimen (44, 56) and/or an isothermal approach (56). For instance, we cannot exclude the possibility that the rate of HA induced adaptations were different between groups across the 7 day period. We also cannot exclude the possibility that the grafted subjects may have continued to improve their heat loss capacity had we used a longer HA regimen. Thus, the conclusions drawn herein are constrained to the HA regimen utilized, as well as the range of BSA grafted (17-75%) that were studied. Furthermore, it should be noted that by measuring whole-body sweat rate from changes in nude body weight pre- to post- exercise, we were unable to provide insights regarding HA induced shifts in sweating dynamics that may be occurring during exercise (e.g., the internal temperature threshold for the onset of sweating and the rate of increase in sweating per increase in body temperature following that threshold). Despite these limitations, the current study provides an important benchmark, indicating that HA can improve heat tolerance and heat dissipation in burn survivors with grafted skin. Therefore, further work is required in order to identify whether the maximum achievable level of adaptation is altered by grafted skin.

Perspectives and significance

Due to medical advances, improvements in survival following a burn injury have resulted in a shift in medical treatment from issues involving mortality to those regarding rehabilitation, quality of life, and returning to work (42). It is clear that ambient temperature and the ability to regulate body temperature affects such factors in burn survivors. For instance, upwards to 74% of burn survivors have subjective intolerance to hot temperatures, which continue many years, if not indefinitely, after burn injury (29). This is not inconsequential, as ambient temperature and humidity can be a barrier in returning to work following such an injury (22). These subjective measures are in line with the findings that heat dissipation is impaired in burn survivors (4, 25, 27, 54). Importantly, the current study demonstrates that impairments in both heat dissipation and heat tolerance can be, at least partially, mitigated by short-term HA. Such findings indicate that the ability to adapt to heat is possible despite burn injuries and that HA or natural acclimatization (e.g., as would occur during the summer) is an effective strategy for improving heat tolerance, safety, and comfort in hot environments that are typically encountered during both work and recreation. Notably however, impairments in heat dissipation remain evident even following HA. Thus, caution and medical oversight should still be used when burn survivors with grafted skin undertake work and/or exercise in hot conditions, especially in those with greater than 40% BSA grafted.

Conclusions

The present study indicates that a short-term, 7 day HA regimen improves heat tolerance and heat dissipation in burn survivors with grafted skin. Responses classically indicative of HA were observed in burn survivors and non-burned individuals alike, which included improvements in heat exercise tolerance, increases in plasma volume, a higher sweat rate for a given increase in internal temperature, attenuated increases in internal temperature during exercise, and lower sweat electrolyte concentrations, ungrafted skin temperatures, and perceptions of warmth and perceived exertion. Interestingly, the magnitudes of the HA induced adaptations were not different between groups. Collectively, these data indicate that HA is a useful tool for improving heat tolerance and heat dissipation in burn survivors. Furthermore, within the scope of the HA regimen employed herein, these data suggest that the degree of adaptation with HA in ungrafted skin is independent of the body surface area available for heat dissipation.

Acknowledgements and Disclosures

We would like to thank the subjects for participating in our study. We would also like to thank Jena Kern, RN, Naomi Kennedy, RN, Linda Eggert, RN, Diane Bedenkop, RN, Gary Purdue, MD, R. Matthew Brothers, PhD, Jiexiu Zhao, PhD, and Kim Hubing for their technical assistance. This study was supported by awards from the National Institutes of Health (R01GM068865, F32AG04328). There are no conflicts of interest to report.

References

1. **Allan J, and Wilson C**. Influence of acclimatization on sweat sodium concentration. *J Appl Physiol* 30: 708-712, 1971.

2. **Association AB**. American Burn Assocation National Burn Repository (2006 report) Chicago: 2007.

3. **Baker LB, Stofan JR, Hamilton AA, and Horswill CA**. Comparison of regional patch collection vs. whole body washdown for measuring sweat sodium and potassium loss during exercise. *Journal of Applied Physiology* 107: 887-895, 2009.

4. **Ben-Simchon C, Tsur H, Keren G, Epstein Y, and Shapiro Y**. Heat tolerance in patients with extensive healed burns. *Plast Reconstr Surg* 67: 499-504, 1981.

5. **Binkley HM, Beckett J, Casa DJ, Kleiner DM, and Plummer PE**. National Athletic Trainers' Association Position Statement: Exertional Heat Illnesses. *J Athl Train* 37: 329-343, 2002.

6. **Borg GA**. Perceived exertion as an indicator of somatic stress. *Scand J Rehabil Med* 2: 92-98, 1970.

7. **Buono MJ, Martha SL, and Heaney JH**. Peripheral sweat gland function is improved with humid heat acclimation. *Journal of Thermal Biology* 34: 127-130, 2009.

8. **Cancio LC, Horvath EE, Barillo DJ, Kopchinski BJ, Charter KR, Montalvo AE, Buescher TM, Brengman ML, Brandt M-M, and Holcomb JB**. Burn support for Operation Iraqi Freedom and related operations, 2003 to 2004. *Journal of Burn Care & Research* 26: 151-161, 2005.

9. **Candas V, Libert JP, and Vogt JJ**. Influence of air velocity and heat acclimation on human skin wettedness and sweating efficiency. *J Appl Physiol* 47: 1194-1200, 1979.

10. **Casa DJ**. Exercise in the Heat. II. Critical Concepts in Rehydration, Exertional Heat Illnesses, and Maximizing Athletic Performance. *J Athl Train* 34: 253-262, 1999.

11. **CDC**. Mass Casualities: Burn. In: *Injury Fact Sheets*2007.

12. **Cheung SS, and McLellan TM**. Heat acclimation, aerobic fitness, and hydration effects on tolerance during uncompensable heat stress. *J Appl Physiol* 84: 1731-1739, 1998.

13. **Cohen JS, and Gisolfi CV**. Effects of interval training on work-heat tolerance of young women. *Medicine and science in sports and exercise* 14: 46, 1982.

14. **Cramer MN, and Jay O**. Selecting the correct exercise intensity for unbiased comparisons of thermoregulatory responses between groups of different mass and surface area. *Journal of Applied Physiology* 116: 1123-1132, 2014.

15. **Davis SL, Shibasaki M, Low DA, Cui J, Keller DM, Purdue GF, Hunt JL, Arnoldo BD, Kowalske KJ, and Crandall CG**. Skin grafting impairs postsynaptic cutaneous vasodilator and sweating responses. *Journal of burn care & research: official publication of the American Burn Association* 28: 435, 2007.

16. **Davis SL, Shibasaki M, Low DA, Cui J, Keller DM, Purdue GF, Hunt JL, Arnoldo TB, Kowalske KJ, and Crandall CG**. Impaired cutaneous vasodilation and sweating in grafted skin during whole-body heating. *J Burn Care Res* 28: 427-434, 2007.

17. **Davis SL, Shibasaki M, Low DA, Cui J, Keller DM, Wingo JE, Purdue GF, Hunt JL, Arnoldo BD, and Kowalske KJ**. Sustained impairments in cutaneous vasodilation and sweating in grafted skin following long-term recovery. *Journal of burn care & research: official publication of the American Burn Association* 30: 675, 2009.

18. **De Dear R, and Brager GS**. Developing an adaptive model of thermal comfort and preference. *Center for the Built Environment* 1998.

19. **Dill DB, Hall FG, and T. EH**. Changes in Composition of Sweat during Acclimatization to Heat. *Am J Physiol* 123: 412-419, 1938.

20. **Dubois D, and Dubois EF**. A formula to estimate the approximate surface area if height and weight be known. *Arch Intern Med* 73: 863-871, 1916.

21. **Eichna LW, Park CR, Nelson N, Horvath SM, and Palmes ED**. Thermal regulation during acclimatization in a hot, dry (desert type) environment. *Am J Physiol* 163: 585-597, 1950.

22. **Esselman PC, Wiechman Askay S, Carrougher GJ, Lezotte DC, Holavanahalli RK, Magyar-Russell G, Fauerbach JA, and Engrav LH**. Barriers to return to work after burn injuries. *Archives of physical medicine and rehabilitation* 88: S50-S56, 2007.

23. **Fox R, Goldsmith R, Kidd D, and Lewis H**. Blood flow and other thermoregulatory changes with acclimatization to heat. *The Journal of physiology* 166: 548-562, 1963.

24. **Gagnon D, Jay O, and Kenny GP**. The evaporative requirement for heat balance determines whole-body sweat rate during exercise under conditions permitting full evaporation. *J Physiol* 591: 2925-2935, 2013.

25. **Ganio MS, Gagnon D, Stapleton J, Crandall CG, and Kenny GP**. Effect of human skin grafts on whole-body heat loss during exercise heat stress: A case report. *Journal of Burn Care & Research* 34: e263-e270, 2013.

26. **Ganio MS, Pearson J, Schlader ZJ, Brothers RM, Lucas RA, Rivas E, Kowalske KJ, and Crandall CG**. Aerobic Fitness Is Disproportionately Low in Adult Burn Survivors Years After Injury. *Journal of burn care & research: official publication of the American Burn Association* 2013.

27. **Ganio MS, Schlader ZJ, Pearson J, Lucas RA, Gagnon D, Rivas E, Kowalske KJ, and Crandall CG**. Non-grafted skin surface area best predicts core temperature responses in burned individuals *Med Sci Sport Exer* In Press: 2015.

28. **Gore CJ, Rodriguez FA, Truijens MJ, Townsend NE, Stray-Gundersen J, and Levine BD**. Increased serum erythropoietin but not red cell production after 4 wk of intermittent hypobaric hypoxia (4,000–5,500 m). *Journal of Applied Physiology* 101: 1386-1393, 2006.

29. **Holavanahalli RK, Helm PA, and Kowalske KJ**. Long-term outcomes in patients surviving large burns: the skin. *Journal of Burn Care & Research* 31: 631-639, 2010.

30. **Inoue Y, Havenith G, Kenney WL, Loomis JL, and Buskirk ER**. Exercise-and methylcholine-induced sweating responses in older and younger men: effect of heat acclimation and aerobic fitness. *Int J Biometeorol* 42: 210-216, 1999.

31. **Jay O, Bain AR, Deren TM, Sacheli M, and Cramer MN**. Large differences in peak oxygen uptake do not independently alter changes in core temperature and sweating during exercise. *Am J Physiol Regul Integr Comp Physiol* 301: R832-841, 2011.

32. **Khudaiberdiev M, Sultanov F, and Pokormyakha L**. Perception of temperature elevation in human seasonal heat adaptation. *Neuroscience and behavioral physiology* 22: 236-240, 1992.

33. **Lorenzo S, Halliwill JR, Sawka MN, and Minson CT**. Heat acclimation improves exercise performance. *J Appl Physiol* 109: 1140-1147, 2010.

34. **Lorenzo S, and Minson CT**. Heat acclimation improves cutaneous vascular function and sweating in trained cyclists. *J Appl Physiol* 109: 1736-1743, 2010.

35. **McEntire SJ, Chinkes DL, Herndon DN, and Suman OE**. Temperature responses in severely burned children during exercise in a hot environment. *Journal of burn care & research: official publication of the American Burn Association* 31: 624-630, 2009.

36. **Mekjavic IB, and Rempel ME**. Determination of esophageal probe insertion length based on standing and sitting height. *J Appl Physiol* 69: 376-379, 1990.

37. **Nadel ER, Pandolf KB, Roberts MF, and Stolwijk JA**. Mechanisms of thermal acclimation to exercise and heat. *J Appl Physiol* 37: 515-520, 1974.

38. **Nielsen B, Hales JRS, Strange S, Christensen NJ, Warberg J, and Saltin B**. Human Circulatory and Thermoregulatory Adaptations with Heat Acclimation and Exercise in a Hot, Dry Environment. *J Physiol* 460: 467-485, 1993.

39. **Nielsen B, Strange S, Christensen NJ, Warberg J, and Saltin B**. Acute and adaptive responses in humans to exercise in a warm, humid environment. *Pflugers Arch* 434: 49-56, 1997.

40. **Nishi Y**. Measurement of thermal balance in man. In: *Thermal physiology and comfort*, edited by Cena K, and Clark J. New York: Elsevier, 1981.

41. **Patterson MJ, Stocks JM, and Taylor NA**. Sustained and generalized extracellular fluid expansion following heat acclimation. *The Journal of physiology* 559: 327-334, 2004.

42. **Pereira C, Murphy K, and Herndon D**. Outcome measures in burn care: is mortality dead? *Burns* 30: 761-771, 2004.

43. **Pivarnik JM, and Senay LC**. Effect of endurance training and heat acclimation on perceived exertion during exercise. *J Cardiopulm Rehabil* 6: 499-504, 1986.

44. **Poirier MP, Gagnon D, Friesen BJ, Hardcastle SG, and Kenny GP**. Whole-Body Heat Exchange during Heat Acclimation and Its Decay. *Medicine and science in sports and exercise* 2014.

45. **Roberts MF, Wenger CB, Stolwijk JAJ, and Nadel ER**. Skin Blood-Flow and Sweating Changes Following Exercise Training and Heat Acclimation. *J Appl Physiol* 43: 133-137, 1977.

46. **Robinson S, Turrell ES, Belding HS, and Horvath SM**. Rapid acclimatization to work in hot climates. *Am J Physiol* 140: 168-176, 1943.

47. **Roskind JL, Petrofsky J, Lind AR, and Paletta FX**. Quantitation of thermoregulatory impairment in patients with healed burns. *Ann Plast Surg* 1: 172-176, 1978.

48. **Sakson JA**. A simplified chart for estimating burn areas. *The American Journal of Surgery* 98: 693-694, 1959.

49. **Sawka MN, Leon LR, Montain SJ, and Sonna LA**. Integrated physiological mechanisms of exercise performance, adaptation, and maladaptation to heat stress. *Comprehensive Physiology* 1: 1883-1928, 2011.

50. **Sawka MN, Pandolf KB, Avellini BA, and Shapiro Y**. Does heat acclimation lower the rate of metabolism elicited by muscular exercise? *Aviat Space Environ Med* 54: 27-31, 1983.

51. **Schlader ZJ, Simmons SE, Stannard SR, and Mundel T**. The independent roles of temperature and thermal perception in the control of human thermoregulatory behavior. *Physiol Behav* 103: 217-224, 2011.

52. **Sciences NIoGM**. Fact Sheet: Trauma, Shock, Burn, and Injury: Facts and Figures http://www.nigms.nih.gov/Publications/trauma_burn_facts.htm. [February, 2008].

53. **Senay L, Mitchell D, and Wyndham C**. Acclimatization in a hot, humid environment: body fluid adjustments. *J Appl Physiol* 40: 786-796, 1976.

54. **Shapiro Y, Epstein Y, Ben-Simchon C, and Haggai T**. Thermoregulatory responses of patients with extensive healed burns. *J Appl Physiol* 53: 1019-1022, 1982.

55. **Sunderland C, Morris JG, and Nevill M**. A heat acclimation protocol for team sports. *British journal of sports medicine* 42: 327-333, 2008.

56. **Taylor NA**. Human heat adaptation. *Comprehensive Physiology* 2014.

57. **Toner MM, Drolet LL, and Pandolf KB**. Perceptual and Physiological-Responses during Exercise in Cool and Cold Water. *Percept Mot Skills* 62: 211-220, 1986.

58. **Weller AS, Linnane DM, Jonkman AG, and Daanen HA**. Quantification of the decay and re-induction of heat acclimation in dry-heat following 12 and 26 days without exposure to heat stress. *European journal of applied physiology* 102: 57-66, 2007.

59. **Wingo JE, Low DA, Keller DM, Davis SL, Kowalske KJ, Purdue GF, Hunt JL, and Crandall CG**. Heat acclimation of an adult female with a large surface area of grafted skin. *J Burn Care Res* 29: 848-851, 2008.

60. **Wolf SE, Kauvar DS, Wade CE, Cancio LC, Renz EP, Horvath EE, White CE, Park MS, Wanek S, and Albrecht MA**. Comparison between civilian burns and combat burns from Operation Iraqi Freedom and Operation Enduring Freedom. *Annals of surgery* 243: 786, 2006.

61. **Wyndham CH**. Effect of acclimatization on the sweat rate-rectal temperature relationship. *J Appl Physiol* 22: 27-30, 1967.

Tables

Table 1: Subject characteristics (mean ± SD).

	Burn survivors with grafted skin		
	17-40% BSA Grafted	>40% BSA Grafted	Control
Number of subjects (male/female)	19 (12/7)	15 (8/7)	9 (4/5)
Years post burn injury	20.8 ± 15.8	11.8 ± 9.2 ‡	--
Median (range)	20.8 (1.2 - 51.0)	9.2 (2.0 - 27.1)	--
Percentage of BSA Grafted (%)	30 ± 7	54 ± 11 ‡	--
Median (range)	31 (17 - 40)	49 (42 - 75)	--
Absolute BSA Grafted (m^2)	0.59 ± 0.17	1.02 ± 0.21 ‡	--
Absolute BSA Ungrafted (m^2)	1.36 ± 0.21 *	0.89 ± 0.24 ‡ *	1.87 ± 0.16
Weight (kg)	82.9 ± 14.6	78.0 ± 15.2	75.0 ± 12.1
Height (cm)	170 ± 13	172 ± 8	172 ± 7
Age (y)	40 ± 12	33 ± 11	32 ± 10
Peak oxygen uptake (L/min)	2.5 ± 0.9	2.5 ± 1.0	2.9 ± 0.8

BSA, Body surface area; ‡ different from 17-40% group ($P \leq 0.059$); * different from control ($P < 0.001$)

Figure Legends

Figure 1: Absolute (top) and relative to body weight (bottom) rates of metabolic heat production (H_{prod}) during exercise pre- and post- heat acclimation (HA) in non-burned control subjects (n=9), and burn survivors with 17-40% body surface area (BSA) grafted (n=19) and >40% BSA grafted (n=15) (mean ± SD). † main effect of HA (P≤0.030); group x HA interaction: P≥0.704.

Figure 2: Heat exercise tolerance pre- (top) and post- heat acclimation (bottom) in non-burned, control subjects (n=9), and burn survivors with 17-40% body surface area (BSA) grafted (n=19) and >40% BSA grafted (n=15).

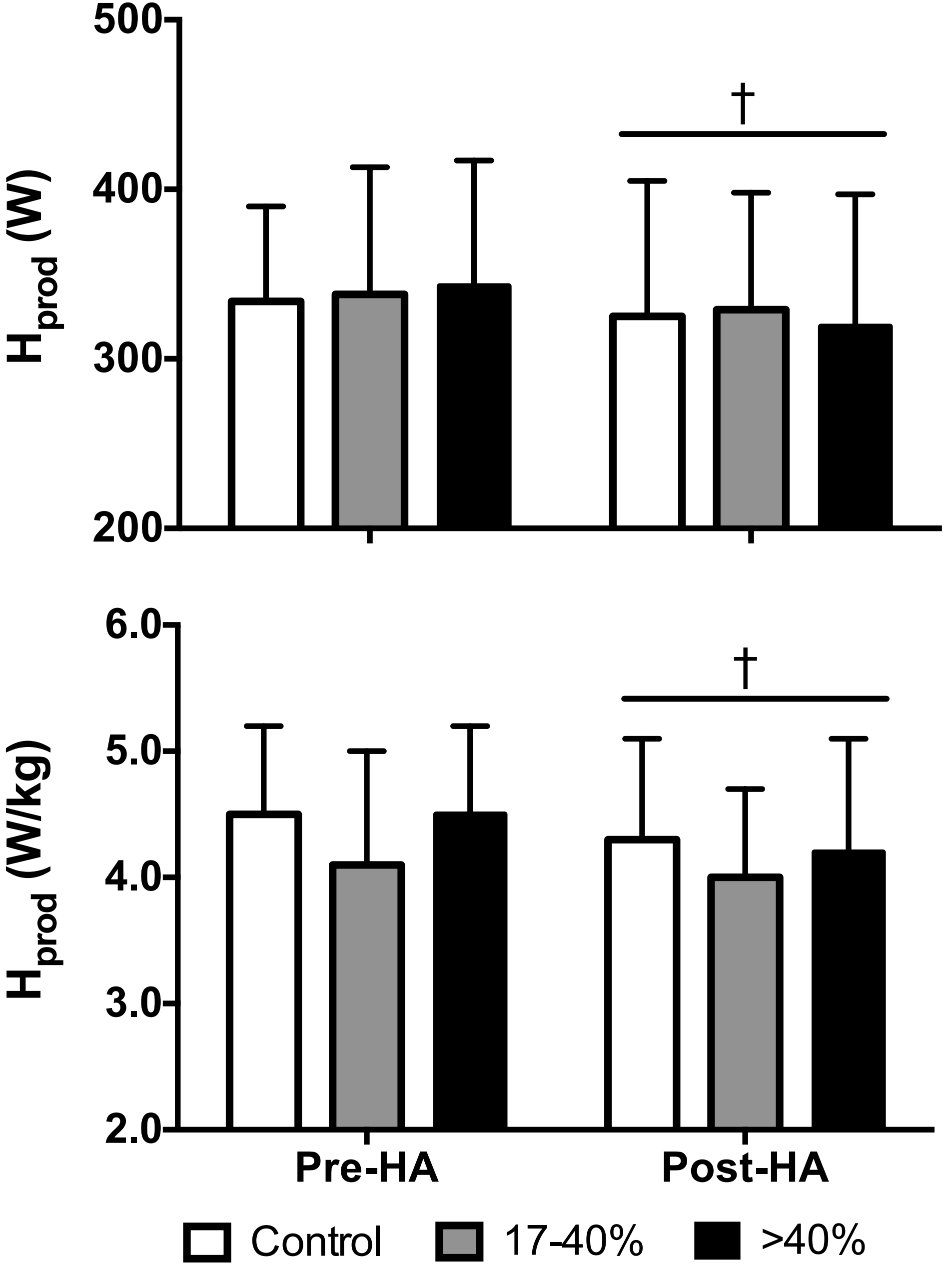
Figure 3: The change (Δ) in internal temperature during exercise (top) and absolute skin temperatures at ungrafted (bottom, left) and grafted (bottom, right) skin locations at the end of exercise pre- and post- heat acclimation (HA) in non-burned, control subjects (n=9), and burn survivors with 17-40% body surface area (BSA) grafted (n=19) and >40% BSA grafted (n=15) (mean ± SD). * different from control (P≤0.031); ‡ different from 17-40% (P≤0.029); † main effect of HA (P≤0.004); group x HA interaction: P≥0.417.

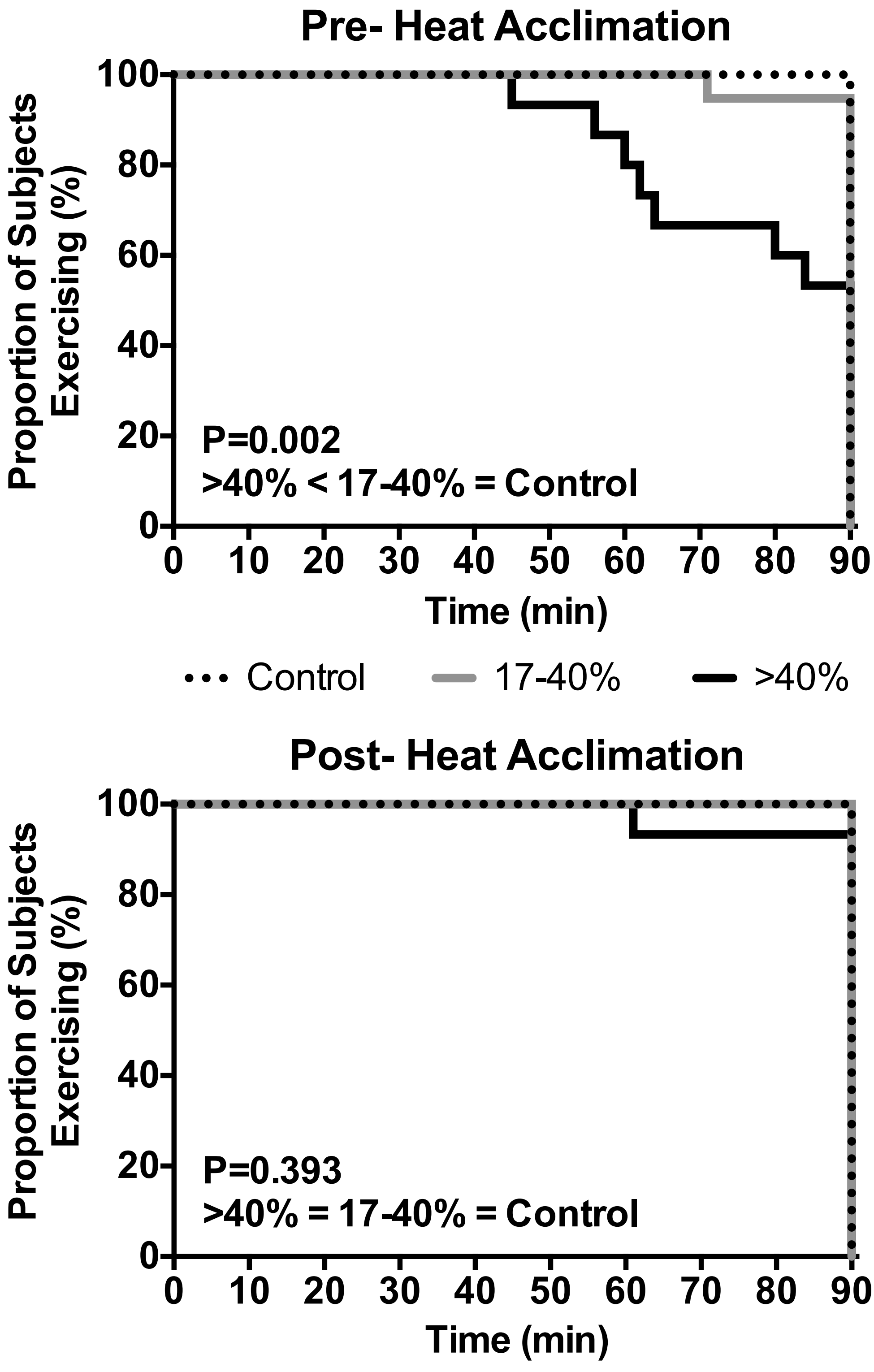
Figure 4: Heart rate at the end of exercise (top) and plasma volume (bottom) pre- and post- heat acclimation (HA) in non-burned, control subjects (n=9), and burn survivors with 17-40% body surface area (BSA) grafted (n=19) and >40% BSA grafted (n=15) (mean ± SD). * different from control (P≤0.006); ‡ different from 17-40% (P≤0.009); † main effect of HA (P≤0.011); group x HA interaction: P≥0.199.

Figure 5: Whole-body sweat rate, expressed as absolute (in L/h, top, left) and relative to the absolute body surface area (BSA) of ungrafted skin (in L/h/m^2, top, right), as well as whole-body sweat rate relative to increases in internal temperature, expressed as absolute (in L/h/°C, bottom, left) and relative to the absolute BSA of ungrafted skin (in L/h/°C/m^2, bottom, right) pre- and post- heat acclimation (HA) in non-burned, control subjects (n=9), and burn survivors with 17-40% body surface area (BSA) grafted (n=19) and >40% BSA grafted (n=15) (mean ± SD). * different from control (P≤0.049); ‡, different from 17-40% (P≤0.022); †, main effect of HA (P≤0.005); group x HA interaction: P≥0.513.

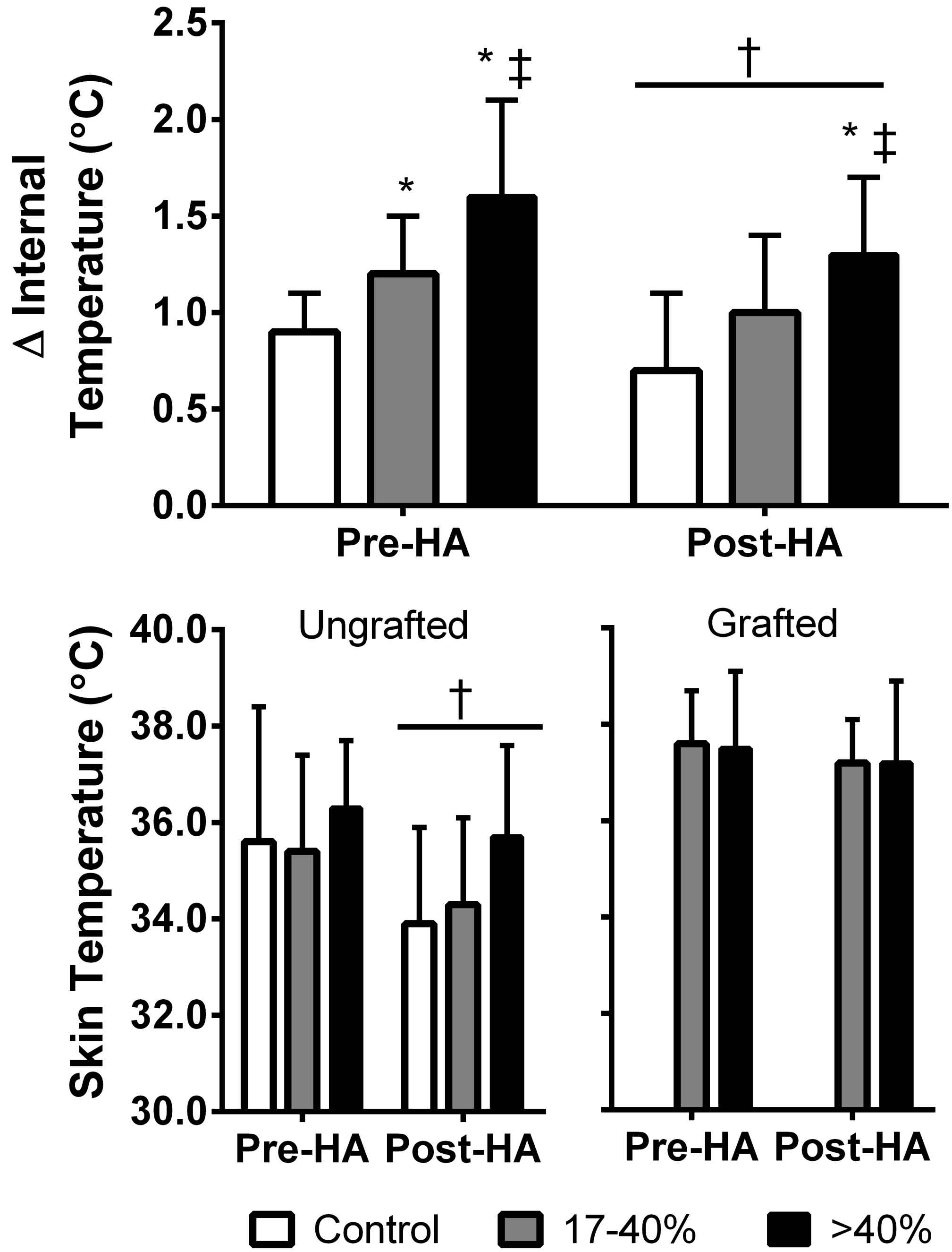
Figure 6: Ratings of perceived exertion (RPE) (left) and thermal perception (right) at the end of exercise pre- and post- heat acclimation (HA) in non-burned, control subjects (n=9), and burn survivors with 17-40% body surface area (BSA) grafted (n=19) and >40% BSA grafted (n=15) (mean ± SD). * different

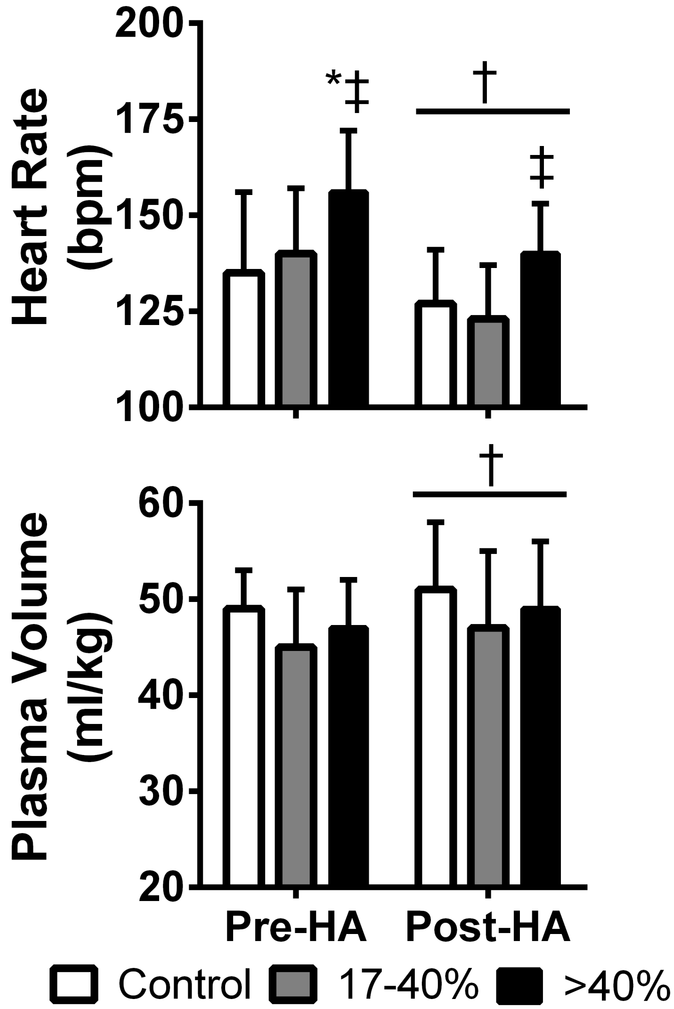
from control ($P \leq 0.023$); ‡ different from 17-40% ($P \leq 0.004$); † main effect of HA ($P \leq 0.001$); group x HA interaction: $P \geq 0.165$.


500
400
300
200
H_{prod} (W)
†
6.0
5.0
4.0
3.0
2.0
H_{prod} (W/kg)
†
Pre-HA
Post-HA
Control
17-40%
>40%

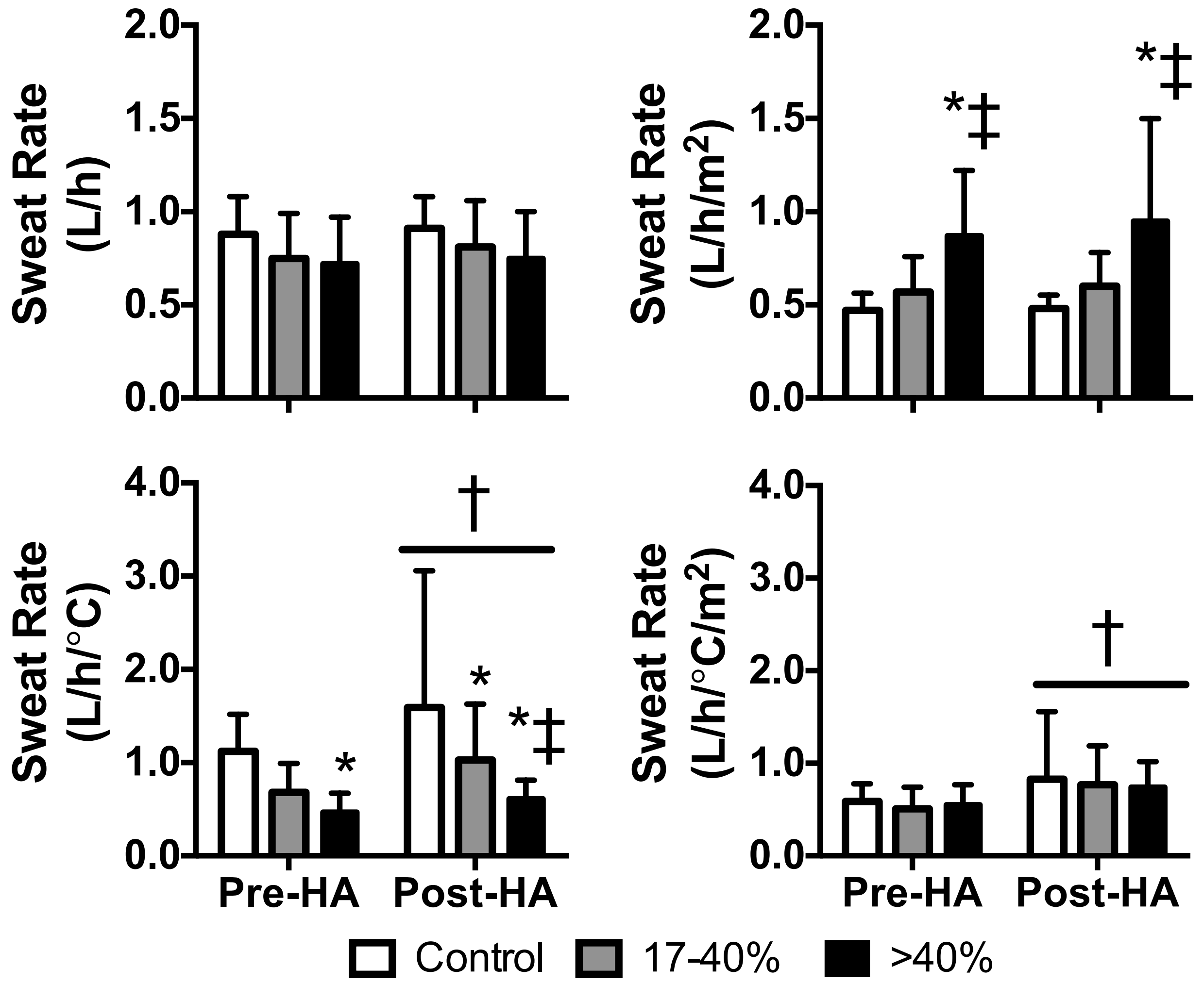


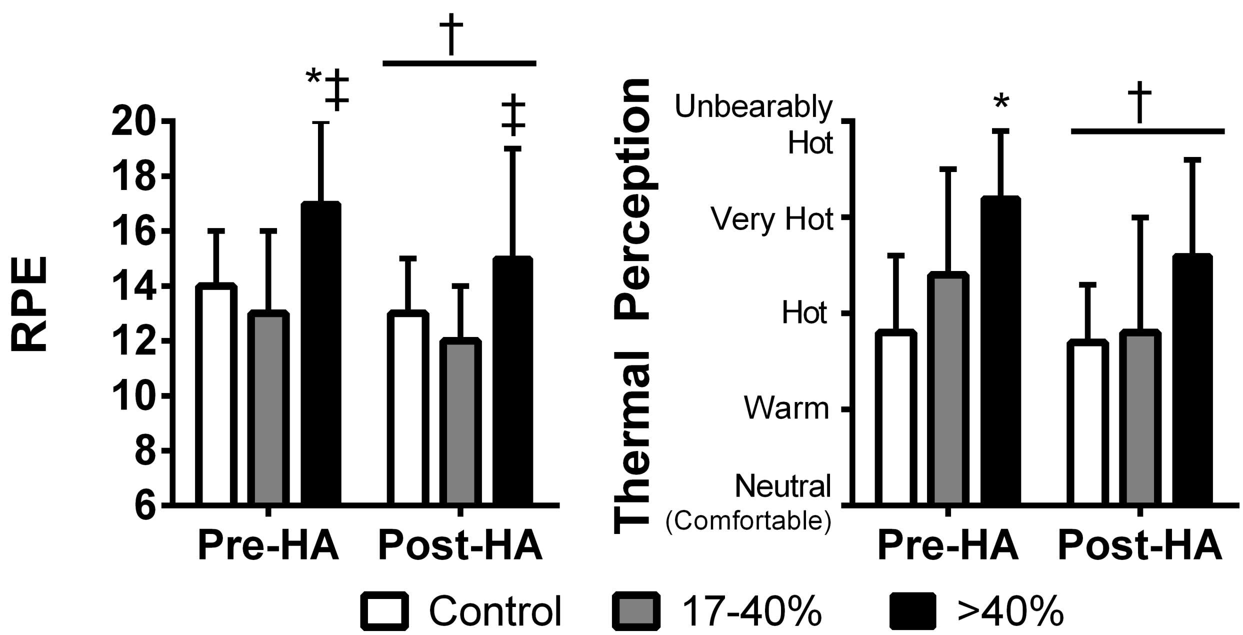
Pre- Heat Acclimation
Proportion of Subjects Exercising (%)
100
80
60
40
20
0
P=0.002
>40% < 17-40% = Control
0 10 20 30 40 50 60 70 80 90
Time (min)
Control
17-40%
>40%
Post- Heat Acclimation
Proportion of Subjects Exercising (%)
100
80
60
40
20
0
P=0.393
>40% = 17-40% = Control
0 10 20 30 40 50 60 70 80 90
Time (min)


Δ Internal Temperature (°C)
2.5
2.0
1.5
1.0
0.5
0.0
*
* ‡
†
* ‡
Pre-HA
Post-HA
Skin Temperature (°C)
40.0
38.0
36.0
34.0
32.0
30.0
Ungrafted
Grafted
†
Pre-HA
Post-HA
Pre-HA
Post-HA
Control
17-40%
>40%



Heart Rate (bpm)
200
175
150
125
100
*‡
†
‡
Plasma Volume (ml/kg)
60
50
40
30
20
†
Pre-HA
Post-HA
Control
17-40%
>40%


Sweat Rate (L/h)
Sweat Rate (L/h/m2)
Sweat Rate (L/h/°C)
Sweat Rate (L/h/°C/m2)
2.0
1.5
1.0
0.5
0.0
4.0
3.0
2.0
1.0
0.0
*‡
*
†
Pre-HA
Post-HA
Control
17-40%
>40%



RPE
20
18
16
14
12
10
8
6
*‡
†
‡
Pre-HA
Post-HA
Thermal Perception
Unbearably Hot
Very Hot
Hot
Warm
Neutral
(Comfortable)
*
†
Pre-HA
Post-HA
Control
17-40%
>40%